EBioMedicine 2 (2015) 1014–1015

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

HPV Vaccination and Complex Regional Pain Syndrome: Lack of Evidence

Cindy M. Weinbaum[a], Maria Cano[b]

[a] Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, USA
[b] Immunization Safety Office, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30329, USA

Many studies have documented the reduction of HPV vaccine type prevalence, cervical lesions, and genital warts in adolescent girls in the years since the introduction of the first HPV vaccine in 2006 (Markowitz et al., 2014; Hariri et al., 2015; Smith et al., 2015). In addition, HPV vaccines have been found to be quite safe: clinical trials and numerous post-licensure safety studies have found no consistent evidence of causal association of HPV vaccination with prespecified health conditions including Guillain–Barré syndrome, stroke, venous thromboembolism, appendicitis, seizures, allergic reactions, anaphylaxis, autoimmune disorders, or a variety of neurologic conditions (Markowitz et al., 2014). However, a number of countries have received, and continue to receive, reports alleging the association of HPV vaccination with a variety of adverse health events, many of which have been systematically investigated and no causal relationships found (Wilson et al., 2015). Reports have engendered a spectrum of immunization program responses (Wilson et al., 2015). In 2013, subsequent to a concern about Complex Regional Pain Syndrome (CRPS) after receipt of HPV 16/18 vaccine, Japan temporarily suspended the national HPV vaccination recommendation. In this issue of EBioMedicine, the risk of CRPS after receipt of HPV 16/18 vaccine is explored in a study by Huygen et al. (2015).

CRPS is a condition of chronic, severe, often burning pain, usually in one or more extremities, that is often accompanied by swelling, skin discoloration, allodynia, abnormal sweating, and impaired motor function in the affected area. The pathogenesis of CRPS has not been definitively determined; CRPS develops following trauma or injury in over 90% of cases. In Japan, a 40-person case-series of peripheral sympathetic nerve dysfunction in adolescent girls after HPV vaccination was described; 18 of the cases were considered to have CRPS (Kinoshita et al., 2014). More research into the possible association of HPV vaccination and CRPS is needed, and Huygen et al. used the worldwide GSK safety database, a proprietary passive reporting system, to conduct such research (Huygen et al., 2015).

Huygen identified 18,391 adverse event reports regarding persons who received HPV 16/18 vaccine (Huygen et al., 2015). Of these, 17 were reports of CRPS; 5 were classified as confirmed CRPS. Additional database searches were conducted to assess the possibility that different pain-related diagnostic codes may include patients with CRPS; no additional cases were identified. Huygen concludes that evidence suggesting an increased risk for CRPS after HPV 16/18 vaccination is lacking. The uncertainty in Huygen's observed vs expected analysis illustrates the challenge of using a spontaneous reporting system, in which the reported fraction is unknown, to quantify an adverse event after immunization (AEFI).

The voluntary, spontaneous reporting system analyzed is by its nature incomplete. However, such systems are often used to identify "signals" of possible adverse events after vaccination. In the United States, the Vaccine Adverse Event Reporting System (VAERS) is a national vaccine safety monitoring system co-administered by the U.S. Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA). We searched VAERS to explore how US-reported data compared to the data used by Huygen et al.

VAERS receives spontaneous reports of AEFI from healthcare providers, manufacturers, the public, and others. Signs and symptoms of AEFI are coded by trained personnel and entered into a database using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized medical terminology, which was also used in the Huygen et al. database (Huygen et al., 2015). VAERS data are publicly available (VAERS: Vaccine Adverse Event Reporting System, n.a.). Between 2006 (when the first HPV vaccine was licensed in the United States), and July 23, 2015 when we conducted our VAERS search, VAERS had received 31,935 reports of AEFI following HPV vaccination. Reflecting the approximately 1% of HPV vaccines distributed in the U.S. that have been bivalent vaccine, approximately 1% of VAERS reports (n = 215) reported receipt of bivalent HPV vaccine. Over 67 million doses of HPV vaccine have been distributed in the United States (Reference: Frequently Asked Questions about HPV Vaccine Safety, US Centers for Disease Control and Prevention, March 30 2015. http://www.cdc.gov/vaccinesafety/Vaccines/HPV/hpv_faqs.html#five. Accessed August 20, 2015.).

We searched for US, primary reports of CRPS reported to VAERS after receipt of any HPV vaccine (HPV2, HPV4, HPV9, and HPV of unknown manufacturer) using the MedDRA terms, "complex regional pain syndrome" and "mononeuropathy multiplex". We identified 22 (0.07%) reports that met the search criteria for CRPS, similar to the fraction of CRPS among reports in the GSK database (0.09%). In 21 reports, the patient had received quadrivalent HPV vaccine; one report was for bivalent

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.07.003.
E-mail addresses: cweinbaum@cdc.gov (C.M. Weinbaum), mcano@cdc.gov (M. Cano).

http://dx.doi.org/10.1016/j.ebiom.2015.08.030

HPV vaccine. The median age of persons with CRPS was 15 years (range 12–19 years); and 21 (91%) were female.

Passive reporting systems such as VAERS and GSK's have a number of strengths, including their broad scope and timely reporting. They can identify disproportionately reported health events after HPV vaccination, but they have significant limitations including over- or under-reporting, biased reporting, and inconsistent quality and completeness of reports. Huygen et al. found that 35% of CRPS case reports in their database were received after the initial case in Japan was reported in the media; increased reporting of HPV vaccine safety concerns after media attention has been reported previously (Eberth et al., 2014).

Such databases cannot be used to assess causality between CRPS and receipt of HPV vaccine; such an assessment would require additional data sources. However, CRPS cases have been reported following HPV and other injectable vaccines, and it has been suggested that the reported cases of CRPS following vaccination may simply be a result of the minor trauma from the injection (Richards et al., 2012). Regardless of a possible causal association between HPV vaccine and CRPS, the findings from Huygen and the data from VAERS indicate that such events are rare.

In July 2015, the European Medicines Agency (EMA) announced that their Pharmacovigilance Risk Assessment Committee will be reviewing available data regarding HPV vaccines and CRPS (as well as postural orthostatic tachycardia syndrome) (Anon, n.a.). The EMA review will be a welcome contribution to the scientific foundation for HPV vaccination programs.

Disclosure

The authors declare no conflicts of interest. The authors' work is fully supported by the US Centers for Disease Control and Prevention.

References

EMA to further clarify safety profile of human papillomavirus (HPV) vaccines Press release, (July 13. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002365.jsp&mid=WC0b01ac058004d5c1. Accessed July 29, 2015).

Eberth, J.M., Kline, K.N., Moskowitz, D.A., Montealegre, J.R., Scheurer, M.E., 2014. The role of media and the Internet on vaccine adverse event reporting: a case study of human papillomavirus vaccination. J. Adolesc. Health 54 (3), 289–295 (Mar).

Hariri, S., Bennett, N.M., Niccolai, L.M., Schafer, S., Park, I.U., Bloch, K.C., Unger, E.R., Whitney, E., Julian, P., Scahill, M.W., Abdullah, N., Levine, D., Johnson, M.L., Steinau, M., Markowitz, L.E., HPV-IMPACT Working Group, 2015. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States — 2008–2012. Vaccine 33 (13), 1608–1613 (Mar 24).

Huygen, F., Verschueren, K., McCabe, C., et al., 2015. Investigating reports of complex regional pain syndrome: an analysis of HPV-16/18-adjuvanted vaccine post-licensure data. EBioMedicine http://dx.doi.org/10.1016/j.ebiom.2015.07.003 (http://www.sciencedirect.com/science/article/pii/S2352396415300608).

Kinoshita, T., Abe, R.T., Hineno, A., Tsunekawa, K., Nakane, S., Ikeda, S., 2014. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. Intern. Med. 53 (19), 2185–2200.

Markowitz, L.E., Dunne, E.F., Saraiya, M., et al., 2014. Centers for disease control and prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm. Rep. 63 (No. RR-05), 1–30.

Richards, S., Chalkiadis, Lakshman, R., Buttery, J.P., Crawford, N.W., 2012. Complex regional pain syndrome following immunization. Arch. Dis. Child. 97, 913–915.

Smith, L.M., Strumpf, E.C., Kaufman, J.S., Lofters, A., Schwandt, M., Lévesque, L.E., 2015. The early benefits of human papillomavirus vaccination on cervical dysplasia and anogenital warts. Pediatrics 135 (5), e1131–e1140 (May).

VAERS: Vaccine Adverse Event Reporting System, a. https://VAERS.hhs.gov (Accessed July 23, 2015).

Wilson, Rose, Paterson, Pauline, Chiu, Jeremy, Schulz, William, Larson, Heidi, 2015. HPV Vaccination in Japan: The Continuing Debate and Global Impacts. A Report of the CSIS Global Health Policy Center. CSIS, Washington DC (April. http://csis.org/files/publication/150422_Wilson_HPVVaccination2_Web.pdf. Accessed July 29, 2015).